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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,788	SHAO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8,9 and 24-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *25 and 26* is/are allowed.

6)☒ Claim(s) *4,8,9,24 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/30/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 10/28/04.

Claims 4, 8, 9, and 24-30 remain pending and under consideration in this Office Action.

Specification

Applicant's amendments were sufficient to overcome the objection for embedded hyperlinks and/or other form of browser-executable code.

Compliance with Sequence Rules

Applicant's amendments were sufficient to place Fig. 3 in compliance with the Sequence Rules. However, Fig. 2 appears to contain a sequence in excess of 9 nucleotides that is not identified by SEQ ID NO, and so fails to comply with the requirements of 37 CFR 1.821 through 1.825. More specifically, on page 2 of Fig. 2, the "Query" sequence in the alignment lacks a SEQ ID NO. If this sequence is in the current Sequence Listing, then it must be identified in the or drawing, or in the brief description of the drawing, by the appropriate SEQ ID NO. if the sequence is not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Objections

Applicant's amendments were sufficient to overcome the objection to claims 8, 9, and 27-29 for failing to further limit the subject matter of a previous claim.

Rejections Withdrawn

Applicants amendments to claims 4 and 24 were sufficient to overcome the rejections of claims 4, 8, 9, 24, and 27-30 for indefiniteness.

Applicants amendments to claims 25 and 26 were sufficient to overcome the rejection of these claims under 35 USC 102.

The rejection of claims 4, 8, 9, and 25-30 under 35 USC 101 is withdrawn in view of Applicant's arguments that SEQ ID NOS:1 and 3 could be used as a probe to detect the presence or absence of CYP2D6 genes.

The rejection of claims 25 and 26 under 35 USC 112, first paragraph is withdrawn in view of Applicant's arguments that SEQ ID NOS:1 and 3 could be used as a probe to detect the presence or absence of CYP2D6 genes.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 24 stands rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility which is specific and substantial, or a well established utility.

The claim is drawn to a method of making a polypeptide comprising SEQ ID NO:2. The specification discloses that the polypeptide of SEQ ID NO:2 is related to cytochrome P450 superfamily member CYP2D6. The cytochrome P450 superfamily members are enzymes that function in detoxification and are involved in drug metabolism.

The specification discloses a variety asserted utilities for the recited polypeptide. The specification teaches that it can be used as a model for the development of human therapeutic targets, aid in the identification of therapeutic proteins, and serve as a target for the development of human therapeutic agents that modulate drug-metabolizing enzyme activity in cells and tissues that express the drug-metabolizing enzyme. More particularly, the specification asserts utilities for SEQ ID NO:2 that are related to its activities in drug metabolism, e.g. drug screening assays. CYP2D6 is known to act on a

variety of drugs (listed at paragraph 16), but the specification fails to positively identify any substrate of SEQ ID NO:2, or to assert that any particular substrate is acted on by SEQ ID NO:2. So, further experimentation would be required to determine what is the activity of SEQ ID NO:2, i.e. on what drugs it will act. Moreover, the specification does not establish any nexus between SEQ ID NOS 1-3 and any disease such that one of skill in the art could immediately use SEQ ID NOS 1-3 to develop therapy for any disease or disorder. Given this information, the use of nucleic acids for expression of SEQ ID NO:2 is not a substantial utility according to the Guidelines for Examination of Applications for Compliance With the Utility Requirement because one would have to determine the function of SEQ ID NO:2, or establish a relationship to some disease or disorder, in order to determine its real world use, if any. See MPEP 2107.01(I).

One might argue that the invention has a readily apparent utility because SEQ ID NO:2 is closely related to CYP2D6,and would be expected to act on the same substrates. SEQ ID NO:2 differs from CYP2D6 by a P34S substitution, the deletion of CYP2D6 amino acids 118-168, and M374V and T486S substitutions. See attached sequence alignment. CYP2D6 is very well characterized, and is known to act on a broad variety of substrates (see paragraph 16 of specification). However, a review of the relevant art shows that the scope of substrates accepted by CYP2D6 varies with the allele or ortholog under consideration, and that the effects of sequence changes on CYP2D6 are unpredictable in terms of substrate specificity. For example, Lewis et al (Xenobiotica 27(4): 319-340, 1997) taught that human CYP2D6 acts on debrisoquine whereas mouse CYP2D6 does not, and that human alleles include both poor

metabolizer and extensive metabolizer alleles (see paragraph bridging pages 319 and 320). Also Yu et al (J. Pharm. Exp. Ther. 303(3): 1291-1300, 2002) showed that although wild type human CYP2D6 acts on codeine, the CYP2D6.10 allele does not. Furthermore, although computer generated models of CYP2D6 exist, it was recognized that predictions based on these models should be tested empirically by a variety of approaches including pharmacophore docking, chemical probe analysis, antibody binding site studies, and site directed mutagenesis. See Ellis et al (Biochem. J. 345: 565-571, 2000), paragraph bridging columns 1 and 2 on page 565. For example, although active site models indicated that S304 of CYP2D6 was a critical residue required for ligand binding, Ellis showed by site-directed mutagenesis that it was not. See abstract. Evidence that the 51 amino acid deletion would alter the activity of CYP2D6 comes from DeGroot et al (Chem. Res. Toxicol. 9:1079-1091, 1996) who developed a 3-dimensional model of CYP2D6 based on known crystal structures of bacterial cytochrome P450s. Based on this model, amino acids 118-122 of CYP2D were predicted to interact with substrates (see e.g. page 1089, column 1, last full sentence. Note that these residues are missing from SEQ ID NO:2 as they fall within the deleted region (CYPD2 118-168). Furthermore, the entire predicted C-helix, containing the conserved WXXXR motif is absent from SEQ ID NO:2. See Fig. 1 at page 1081, and page 1082, column 1, lines 7-12. Given the state of the art of predicting the activity of CYP2D6 mutations, as evidenced by Ellis above, one of skill in the art at the time of the invention could not have predicted the effects on enzyme activity of a 51 amino acid deletion that removed from the protein substrate-interacting residues as well as a highly

conserved motif and an entire alpha helix. As a result one of skill in the art would have had to empirically determine if the SEQ ID NO:2 retained any activity at all, and if it did, on which substrates it would act. In other words, further research would be required to determine the real world use of the invention. Accordingly it lacks a substantial utility.

Response to Arguments

Applicant's arguments filed 10/28/04 have been fully considered but they are not persuasive.

Applicant addresses the rejection at pages 5-8 of the response with arguments beginning on page 7. At page 7, Applicant argues that one of skill in the art would easily be able to determine whether or not a drug or a compound is capable of serving as a substrate for the polypeptide of SEQ ID NO:2 based on the structure of DeGroot. This is unpersuasive because the structure of DeGroot is not the structure of SEQ ID NO:2, it is a proposed structure of CYP2D6 based on the structure of bacterial cytochrome P450s. As noted above, SEQ ID NO:2 differs from CYP2D6 by a P34S substitution, the deletion of CYP2D6 amino acids 118-168, and M374V and T486S substitutions. Applicant has not addressed how one could account for the effects on activity of deleting 51 amino acids while also including P34S, M374V, and T486S mutations. How does the structure of DeGroot allow one to predict the substrate specificity of the resulting protein, particularly in view of the fact that deleted residues 118-122 were predicted by DeGroot to interact with substrates? Second, Applicant's assertion that it would be easy to determine whether or not a drug or a compound is

capable of serving as a substrate based on the structure of DeGroot is only a statement of opinion. Applicant fails to provide any logical or evidentiary support, such as the use of the model to accurately predict the substrate specificity of any other enzyme, for this opinion. Third, the fact that one would necessarily have to empirically determine the activity of the protein by screening means that its activity is unknown, and it has no substantial utility for the reasons set forth above.

Applicant appears to argue in the paragraph bridging pages 7 and 8 that the fact that Ellis showed that predictions of substrate activity based on structural models should be tested empirically is at odds with the Examiner's concern that a 51 amino acid deletion might alter the activity of the enzyme. This is unpersuasive. Ellis used site-directed mutagenesis to show that a single amino acid residue, predicted by structural models to be critical for activity, was not required. This points out the fallibility of structural models. It is unclear how this affects the fact that SEQ ID NO:2 differs from CYP2D6 by deletion of 51 amino acids including a conserved WXXXR motif. The Office has shown that the effects of point mutations on CYP2D6 are unpredictable, so it is unclear how one can account for the combined a 51 residue deletion combined with three point mutations, particularly in view of the fact that the art recognized that the predictions based on structural models needed to be tested empirically. Regarding Applicant's request for evidence that the C-helix is not present, the model of DeGroot predicts that the C-helix consists of residues 126-147 of CYP2D6. See Fig. 1 on page 1081. These residues are included in the 51 amino acid deletion and are not present in SEQ ID NO:2.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24 stands rejected under 35 U.S.C. 112, first paragraph. Because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above under 35 U.S.C. 101, one skilled in the art would not know how to use the claimed invention.

Applicant is required to establish only a single utility which is credible, specific and substantial, or well established. In the event that the utility rejection under 35 U.S.C. 101 above is overcome, the following enablement rejection including claim 24 will still apply.

Claims 4, 8, 9, 24, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification while enabling for SEQ ID NOS: 1 and 3, does not reasonably enable the broader scope of all nucleic acids that encode SEQ ID NO:2, nor does it enable methods of making SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining enablement are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Claims 4, 8, 9, and 27-30 embrace nucleic acids encoding the amino acid sequence of SEQ ID NO:2, and claim 24 is drawn to a method of making a polypeptide comprising SEQ ID NO:2. The specification discloses that the polypeptide of SEQ ID NO:2 is related to cytochrome P450 superfamily member CYP2D6. The cytochrome P450 superfamily members are enzymes that function in detoxification and are involved in drug metabolism. As discussed above, the specification fails to assert any specific activity of SEQ ID NO:2 or establish any nexus between SEQ ID NO:2 and any specific disease. Thus one of skill in the art would first have to determine the activity of SEQ ID NO:2, or its relationship to a disease, in order to use SEQ ID NO:2 as intended.

One might argue that such experimentation is not undue in view of the amount of information available concerning CYP2D6, a related polypeptide. SEQ ID NO:2 differs from CYP2D6 by a P34S substitution, the deletion of CYP2D6 amino acids 118-168, and M374V and T486S substitutions. See attached sequence alignment. CYP2D6 is very well characterized, and is known to act on a broad variety of substrates (see

paragraph 16 of specification). However, a review of the relevant art shows that the scope of substrates accepted by CYP2D6 varies with the allele or ortholog under consideration, and that the effects of sequence changes on CYP2D6 are unpredictable in terms of substrate specificity. Lewis et al (Xenobiotica 27(4): 319-340, 1997) taught that human CYP2D6 acts on debrisoquine whereas mouse CYP2D6 does not, and that human alleles include both poor metabolizer and extensive metabolizer alleles (see paragraph bridging pages 319 and 320). Also Yu et al (J. Pharm. Exp. Ther. 303(3): 1291-1300, 2002) showed that although wild type human CYP2D6 acts on codeine, the CYP2D6.10 allele does not.

Ellis et al (Biochem. J. 345: 565-571, 2000) taught that, at the time the invention was filed, there existed in academia and the pharmaceutical industry a great interest in developing a predictive model of the active site CYP2D6, but that this was problematic due to the absence of a crystal structure for any eukaryotic cytochrome P450, let alone a human P450. Ellis goes on to note that computer generated models of the active site of CYP2D6 needed to be validated experimentally using a variety of approaches including pharmacophore docking, chemical probe analysis, antibody binding site studies, and site directed mutagenesis. See paragraph bridging columns 1 and 2 on page 565. For example, although active site models indicated that S304 of CYP2D6 was a critical residue required for ligand binding, Ellis showed by site-directed mutagenesis that it was not. See abstract. This indicates that the state of the art of CYP2D6 structure-functional analysis was unpredictable at the time of filing, despite the existence of theoretical models of its active site. In view of the fact that one of skill in

the art could not accurately predict the effect of a single amino acid substitution on the catalytic activity of CYP2D6, it is highly unlikely that one of skill in the art could predict the effect of the deletion of 51 amino acids from the polypeptide, as in SEQ ID NO: 2. It is also worth noting that Wang et al, (Drug Metab. Disp. 27(3): 385-388, 1997) taught that the P34S and T486S mutations present in SEQ ID NO:2 each decrease the activity of CYP2D6 (see second sentence of paragraph bridging columns 1 and 2 on page 385). So, SEQ ID NO:2 represents a polypeptide comprising 2 mutations with a negative effect on activity, combined with a 51 amino acid deletion (representing about 10% of CYP2D6).

Evidence that the 51 amino acid deletion would alter the activity of CYP2D6 comes from DeGroot et al (Chem. Res. Toxicol. 9:1079-1091, 1996) who developed a 3-dimensional model of CYP2D6 based on known crystal structures of bacterial cytochrome P450s. Based on this model, amino acids 118-122 of CYP2D were predicted to interact with substrates (see e.g. page 1089, column 1, last full sentence. Note that these residues are missing from SEQ ID NO:2 as they fall within the deleted region (CYPD2 118-168). Furthermore, the entire predicted C-helix, containing the conserved WXXXR motif is absent from SEQ ID NO:2. See Fig. 1 at page 1081, and page 1082, column 1, lines 7-12.

Given the state of the art of predicting the activity of CYP2D6 mutations, as discussed above, one of skill in the art at the time of the invention could not have predicted the effects on enzyme activity of combining two deleterious mutations (P34S and T486S) with a 51 amino acid deletion that removed from the protein substrate-

interacting residues as well as a highly conserved motif and an entire alpha helix. As a result one of skill in the art would have had to empirically determine if the SEQ ID NO:2 retained any activity at all, and if it did, on which substrates it would act. One might argue that this would be a simple matter of assaying the known CYP2D substrates. However, as discussed above the effects of a 51 amino acid deletion, including active site residues, are unpredictable with respect to substrate specificity. As set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. In this case, the specification fails to positively identify a single substrate of SEQ ID NO:2, and fails to establish any nexus between SEQ ID NO:2 and any disease or disorder. Absent such guidance or working examples in the specification, in view of the state of the art and the unpredictable nature of the subject matter, even those of the highest level the level of skill in the art would have to perform undue experimentation in order to use the polypeptide encoded by SEQ ID NO:2.

Response to Arguments

Applicant's arguments filed 10/28/04 have been fully considered but they are persuasive only in part.

Applicant considers the enablement rejection at pages 8-10 of the response. The arguments raise the same issues addressed above under 35 USC 101, and were fully addressed there. Applicant argues that it would be easy to determine whether or not a drug or a compound is capable of serving as a substrate based on the structure of DeGroot. However, this statement of opinion only a statement of opinion. Applicant fails to provide any logical or evidentiary support, such as the use of the model to accurately predict the substrate specificity of any other enzyme, for this opinion. Applicant's arguments are based on the availability of a theoretical of a model of CYP2D6, however SEQ ID NO:2 is not CYP2D6, and differs from it substantially as established in the rejection. In view of the unpredictability of cytochrome p450 structure/function relationships as established above, the failure of the specification to identify any substrate of SEQ ID NO:2, the failure to establish any nexus between SEQ ID NO:2 and any disease or disorder, one of skill in the art would have to perform undue experimentation in order to use the polypeptide encoded by SEQ ID NO:2, and the rejection is maintained. Further, the Office has demonstrated that there is no basis for accurately predicting the substrate specificity of SEQ I DNO:2, such that fact that one would necessarily have to empirically determine the activity of the protein by screening means that its activity is unknown, and it has no substantial utility for the reasons set forth above. As such the rejection of claim 24 is maintained in full.

Applicant also argues that the claimed nucleic acids could be used as probes to detect the presence or absence of CYP2D6. This is persuasive as regards SEQ ID NOS: 1 and 3, but is not persuasive as regards the broader scope of all nucleic acids

that encode SEQ ID NO:2. SEQ ID NOS: 1 and 3 comprise several stretches of several hundred base pairs of identity with the known sequences of CYP2D6. Clearly they would function well as probes. However, the genus of sequences that encode SEQ ID NO:2 comprises degenerate versions of SEQ ID NOS: 1 and 3 that have as little as about 65% identity to SEQ ID NO:2, and even less towards some of the known sequences of CYP2D6. The specification does not contemplate the development of probes for the known sequences of CYP2D6 by using degenerate versions of SEQ ID NOS: 1 and 3. Furthermore, when selecting a probe for a known sequence, one of skill in the art generally would choose the best probe for the job, i.e. one with the highest sequence identity. There is no readily apparent reason that one of skill in the art would choose to use a degenerate version of SEQ ID NO:1 or 3 for the job, when SEQ ID NOS: 1 and 3 were available and had large regions of identity with the target. Also, a large fraction of these degenerate probes would be unsuitable for detection of CYP2D6, due to poor specificity. For these reasons, Applicant's argument that the entire genus of sequences encoding SEQ ID NO:2 are enabled for use as probes for the detection of the presence or absence of CYP2D6 is unpersuasive. Applicant is encouraged to limit the claims to SEQ ID NOS: 1 and 3.

Conclusion

Claims 25 and 26 are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Richard Schnizer, Ph.D.

DAVE TRONG NGUYEN
PRIMARY EXAMINER